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REMARKS

Claims 16 to 31 have been rejected under 35 U.S.C. 112 second paragraph as indefinite. It is submitted this rejection is improper and should be withdrawn.

The Examiner states that claims 16, 26 and 28 are rejected because of the phrase "content a first active ingredient" and that phrase is a broad recitation followed by a more narrow recitation. It is submitted the Examiner is in error.

The language of claims 16, 26 and 28 is not the recitation of a first broad substance followed by the recitation of a more narrowly defined substance. The language between that characterized by the Examiner as the broad range and the narrow range is not language like "such as" which was used in *Ex parte Wu*. Rather, here the recitation of the candesartan or one of its esters or salts is the active ingredient. Candesartan and its esters or salts are not used as an example of the active ingredient, at least one of them is the active ingredient.

The phrase "rubber like" in claim 27 has been replaced and a spelling correction has been made to claim 31 with minor grammatical changes.

Claim 16, 17 and 20 to 22 have been rejected under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 5,985,915 to Frangin et al. ("Frangin"). It is submitted this rejection is in error and should be withdrawn.

For a reference to anticipate a claimed invention, that single reference must show each feature recited in the claim and each of those features must be arranged as in the claim (identity). Further, the reference must include an enabling disclosure so that one of ordinary skill in the art can practice the invention (enablement).

It is submitted that Frangin is not an anticipatory reference.

The present invention addresses the problem of providing a form of administration for candesartan and/or esters or salts to overcome the drawbacks of previously oral or intravenous forms of administration. These drawbacks included low bioavailability, hepatic metabolization with toxic byproducts or frequent repeat of application.

Frangin teaches the use of benzofuran derivatives, such as amiodarone, for the prevention of mortality following a myocardial infarction. The examples show tablets or injectable solutions with amiodarone or dronedarone. Clinical studies for amiodarone tables reveal the reduction of mortality. Benzofuran derivatives with antiarrhythmic activity may be combined with another cardioactive agent e.g. ACE-inhibitors, diuretics, angiotensin II inhibitor (like candesartan). Fragin does not teach a transdermal therapeutic system containing candesartan or an ester or salt thereof. A passing mention of a transdermal delivery system does not meet the identity or enablement requirement.

Claims 16 to 22 have been rejected under 35 U.S.C. 103(a) as unpatentable over Frangin. It is submitted this rejection is improper and should be drawn.

The Office Action does not address the limitations of the dependent claims and therefore it is assumed that the references do not suggest these features. The Examiner is requested to apply the reference, if possible, to the dependent claims, by citing where in the reference any of the limitations recited in the dependent claims are shown or suggested. Frangin does not contain any teaching that suggests solving the technical problem of interest by means of transdermal administration.

The Examiner acknowledges that reference differs from the claimed invention by not teaching the specific form of candesartan or its salts but concludes this would have been prima facie obvious to one of ordinary skill in the art.

It is respectfully submitted the Examiner's conclusion of obviousness is not supported. There is nothing to generally indicate that every active ingredient can be administered in the form of a transdermal patch. As such, the Examiner must provide evidence on the record to support either the basic underlying assumption (that all active ingredients can be administered by way of transdermal patch) or specific information showing that these particular compounds have in fact been known to have been administered by transdermal technology. In this regard, the Examiner is called upon to comply with the requirements of 37 C.F.R. 1.104(d)(2).

The Examiner also notes that Frangin is silent as to the teaching of a diuretic or calcium blocker as a second therapeutic agent but relies on the general language of the abstract. It is submitted this is improper. Generalizations do not establish obviousness. If that were the case, very few patents could ever issue.

Claims 16, 17, 19 and 22 were rejected under 35 U.S.C. 103(a) as unpatentable over U.S. Patent No, 5,616,591 to Poss in view of Frangin. It is submitted this rejection is improper and should be withdrawn.

Poss teaches quinoline derivatives useful as angiotensin II inhibitors. Candesartaan is not an quinoline derivative. The focus of this invention is the synthesis of quinoline derivatives. Poss only suggests these quinoline derivatives (column 7, line 49-58; column 8, line 19-23) to be administered oral, intranasal, transdermal, parenteral,... . No examples for transdermal patches with angiotensin II inhibitors are reported. Nor does the reference suggest that any of the preparations of the examples are useful for a transdermal administration. Thus, it is not possible

to obtain a working transdermal patch with candesartan as active ingredient by way of the combination of Poss and Frangin.

Claims 23 to 31 have been rejected under 35 U.S.C. 103(a) as unpatentable over Poss and Frangin in view of U.S. Patent No. 5,464,628 to Jalonen et al. (Jalonen). It is submitted this rejection is also improper and should be withdrawn.

Jalonen teaches substituted imidazole derivatives which are a_2 adrenoceptor antagonists for transdermal administration. Matrix- and reservoir transdermal delivery systems are disclosed.

Candesartan (2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylic acid) is much more complex than Jalonen's imidazole derivatives. It is not obvious that candesartan is suitable for transdermal administration. Neither Frangin, Poss nor Jalonen show that candesartan is suitable for transdermal application.

Jalonen acknowledges that not all therapeutically active substances are suitable for transdermal administration at column 2, starting at lines 13 to 29 which reads as follows:

> Only a minor part of commercially available therapeutically active substances is suitable for transdermal administration due to many different pharmacokinetic and pharmacological reasons. One of the most limiting factors is, however, the physiocochemical properties of the therapeutically active substance itself. For a compound to be able to penetrate the skin it must have both lipophilic (fat soluble)and hydrophilic (water soluble) properties in a suitable proportion. Such a suitable ratio between the lipophilic and hydrophilic properties is not very common for drug substances. The ability of a drug to penetrate through the skin can be predicted by its partition coefficient P in octanol/water. It is known that compounds having an optimal partition coefficient penetrate the skin better than compounds with either higher or lower partition coefficients. This optimal partition coefficient value is different for different kinds of compounds.

Accordingly, any broad conclusions of obviousness are not warranted and the art specifically teaches away from such broad conclusions.

It is submitted that the combination of reference is improper. It is clear that the rejections are based on hindsight reconstruction of one more of the references wherein a reference has been edited or only a minor part of the reference has been considered. As acknowledged by Jalonen, not all therapeutically active substances are suitable for transdermal administration. Therefore, a passing mention, such as in Frangin, of transdermal administration without support by examples showing an operative embodiment cannot be relied upon either for purposes of anticipation or for purposes of obviousness. The mere fact that there is mention in the art of one or more features of the invention does not justify a combination of the references. See *In re Grabiak* 226 U.S.P.Q. 870 (Fed. Cir. 1985).

In view of the foregoing, reconsideration and allowance of the application with claims 16 to 31 are earnestly solicited.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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Dated: August 7, 2002

AMENDMENTS TO THE SPECIFICATION AND CLAIMS SHOWING CHANGES

In the Claims:

27. (Amended) The transdermal therapeutic system of claim 26 wherein the matrix layer comprises a polyacrylate, silicone, polyisobutylene, rubber, [rubber-like synthetic homo-, co- or block polymers] natural or synthetic rubber, butyl rubber, styrene/isoprene copolymer, a polyurethane[s], a copolymer[s] of ethylene, a polysiloxane[s] or a styrene/butadiene copolymer.

31. (Amended) The transdermal therapeutic system of claim 30 wherein the permeation promoter is [elected] selected from the group consisting of monohydric and/or polyhydric aliphatic, cycloaliphatic and/or aromatic-aliphatic alcohols each with up to 8 C atoms, and/or polyethylene glycol; an alcohol/water mixture[s]; saturated and/or unsaturated fatty alcohols each with 8-18 C atoms; a terpene[s]; a mixture[s] of a terpene[s] and ethanol and/or propylene glycol; tea tree oil; a saturated and/or unsaturated cyclic ketone[s]; alkyl methyl sulfoxide[s]; saturated and/or unsaturated fatty acids each with 8-18 C atoms[;], the esters and salts thereof; natural vitamin E; synthetic vitamin E and/or a vitamin E derivative[s]; sorbitan fatty acid esters and ethoxylated sorbitan fatty acid esters; Azone (laurocapram); Azone mixed with an alcohol[s]; urea; 1-alkylpyrrolidone; block copolymers of polyethylene glycol and dimethylsiloxane with cationic groups at one end; folate-polyethylene glycol liposome, proliposome; polyoxyethylene 10 stearyl ether; a mixture of polyoxyethylene 10 stearyl ether and glyceryl dilaurate; dodecyl 2-(N,N-dimethylamino)propanoltetradecanoate and/or dodecyl 2-(N,N-dimethylamino)propionateN-acetylprolinate esters with more than 8 C atoms; nonionic surfactants, esters of polyoxyethylene; ethosome (phospholipid vesicle); dimethyl(arylimino)sulfurane; a mixture of an oleic acid analog[s] and propylene glycol; a

mixture of padimate O, octyl salicylate, octyl methoxycinnamate and laurocapram and/or mixtures thereof.